Risk/benefits of oral retinoids

Panel discussion: Benefit/risk judgments for patients receiving retinoids on a short- and long-term basis

G. D. Weinstein, M.D.: In the last decade many of us have wrestled with the problem of defining benefit/risk judgments for new therapies in dermatology, particularly psoriasis and specifically on the use of methotrexate and PUVA. At this meeting we have seen the situation in which we have both efficacy and toxicity of a drug, and we have to consider the problem: "What are the benefit/risk judgments going to be for patients who will be eligible to receive retinoids for the various diseases?" This is not an easy problem, as I am sure you all realize. One of the big difficulties is that there are many variables that come into play. For some patients, such as those with cystic acne, we are talking about short-term therapy. For patients with diseases such as psoriasis or ichthyosis, it is long-term therapy. We have problems related to age, sex, diagnosis, and which retinoid is being used. We have asked this panel, all of whom have used retinoids in various ways, to start with a statement concerning the benefit/risk judgment and then we will open the subject to all the participants.

H. H. Roenigk, Jr., M.D.: Let me just address one aspect of the problem, namely, the potential liver toxicity. I do not think this is necessarily the most serious problem, especially in dealing with psoriasis. I think that teratogenicity is probably a much more serious problem. But I think that when you try to compare the potential liver toxicity of etretinate with alternative choices that we have, the risk/benefit is probably in the middle. The three major types of systemic therapy which are generally available today for psoriasis are retinoids, PUVA, and methotrexate. Of these, methotrexate probably has much greater potential of producing serious damage to the liver. PUVA probably has no effect whatsoever on the liver, and the retinoids, I would say, probably fall somewhere in the middle. While vitamin A does have an effect on the liver, it was initially thought that the synthetic retinoids were not going to have a similar effect. However, I think that it is now partially clear that there is some storage in the liver. Our own studies presently indicate that liver damage is potentially minimal, but the data are still very preliminary. The fact that it took us 20 years to learn about the liver toxicity of methotrexate, and we still do not know the final answer to this problem, indicates the need for continuous monitoring. The point is that while it may not take that long, it may be 10 years before we know whether etretinate produces significant liver toxicity. However, I do not think that this is a reason to withhold therapy from patients.

L. C. Harber, M.D.: I would like to broaden the remarks of Dr. Roenigk a bit if I may to say that I think the whole concept of a risk/benefit ratio represents our profession at its best or at its worst. It doesn't involve a drug, it involves a one-to-one relationship between a physician at a given time and a patient at a given time and the dialogue that they enter into. Some of the risk factors would make me give different answers to different people at different times. The keystone of any type of dialogue between a physician and a patient is the firm body of scientific knowledge. As it applies to the retinoids, I have no hesitancy, in view of all the toxicity studies which have been discussed today, to actively give the medication to people with the type of cystic acne that was shown. I would have no hesitancy in giving it to the rapid proliferative conditions that were shown by several of the people. On the other hand, there are milder forms of psoriasis, or even some of the forms that were shown today, that I would have reservations on. Now, that is only in terms of the disease. After that, when we talk about people at risk where we do not know the period of time that the risk will perpetuate itself, I think it calls for some very serious thinking and I have no glib answers.

L. A. Goldsmith, M.D.: I guess the question is, "What would I do if I had an unlimited supply of oral retinoids?" My own experience has been with isotretinoin, and I will talk about that. If I were to use the drug for short-term patients with cystic acne and use it to see if one can put a patient with pityriasis rubra pilaris into remission, I could feel good about using the drug, for we already know that there is tremendous potential gain and we have data that the risk is very low. This represents an approach to one group of patients.

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The second group of patients are those with Darier's disease and the various forms of ichthyosis who are really severely limited by their disease in terms of what they can do in school, what they can do in their life, and in their whole outlook to the world. They represent a very challenging group. In general, I put these patients on oral retinoids, especially if they have had various other forms of therapy without good results. However, I am very concerned when I hear about patients with ichthyosis vulgaris and X-linked ichthyosis who are on oral retinoids. At least from my personal point of view, we can treat these two much more common diseases with absolutely benign kinds of therapies with which one really does not worry about risks. I am very concerned about the question of teratogenicity with etretinate. That is a potential time bomb. It will take time for all of us to learn how to use the retinoids. It has taken us a long time to learn how to use steroids. I do not think that we should feel that we know how to use retinoids perfectly, since we have only had them for a short time. I think that we already have a good idea about dose ranges. I am concerned that we have had to wait a long time to find out about the pharmacokinetics of this drug. I think that, since there are going to be second and third generation retinoids coming along, it is going to be really critical to have the pharmacokinetic data very early in the game in the future.

T. P. Nigra, M.D.: In December of 1978, when we first found that seven of our ten patients had triglyceride elevations, I thought that this elevation might be the death knell of isotretinoin as a drug. But I really think that I have changed my mind a lot on this issue. I think that the triglyceride elevation is something that in certain situations we can live with. For instance, if you are going to use the drug only for short periods of time, such as in cystic acne, then I think that one can live with some triglyceride elevation. Nevertheless, short-term elevation can result in acute pancreatitis and eruptive xanthomas.

However, there comes the problem of long-term use of the drug and long-term triglyceride elevation. Here there is a change in the risk/benefit ratio. In our situation, we elected to discontinue the drug on one 50-year-old man who had elevations of both the triglycerides and the cholesterol. We had another 13-year-old boy with Darier's disease, whose data were presented by Dr. Windhorst, in whom we continued the drug. His father had died of a heart attack at the age of 37. When we drew his baseline studies, the boy had type 4 hyperlipoproteinemia. Diet definitely helps his hyperlipoproteinemia, and when he is on his diet his baseline lipid values are within normal limits. When we give him the drug, his lipid levels go up. However, since we have to give him isotretinoin for only 1 week out of every 3 months, we feel that we are adequately dealing with the risk/benefit problem.

When it comes to the problem of teratogenicity, I would like to discuss another patient. We are treating a young lady who has pustular psoriasis of her hands. Her fingers are atrophied as a result of topical steroid therapy. She has used PUVA to the point of neurotoxicity or phototoxicity, methotrexate to the point of ulcers in her mouth, vitamin A to the point of pseudotumor, and the steroids to the point of atrophy. Nothing has worked for her. She is obviously psychologically disabled by her disease. A long time ago I was very anxious to use etretinate on her. But now that teratogenicity has really become obvious, I really think that the risk/benefit ratio is a problem, and even with all of those modalities not working, I would still not use etretinate. Unfortunately, I think she has got to live with her disease.

J. S. Strauss, M.D.: It is interesting to me that there is so much concern about the side effects among those at this conference. This is a healthy situation because we who have had an opportunity to use the drug will have to provide continuing guidance when the drug is initially marketed. Dr. Harber has said we need to look at the risk/benefit ratio very seriously in every patient. These drugs are not, at this point, the treatment of choice for every case of cystic acne or psoriasis. In the management of acne, we are probably in a better position with regard to safety since the current data indicate that smaller dosages can probably be used in the majority of cases requiring retinoid therapy. Furthermore, the course of therapy may be relatively short and remissions may be prolonged. However, I am not sure that we have established the optimal dosage. Another advantage that we have is that we are using isotretinoin and not etretinate, since animal studies have shown that the former is less teratogenic. The retinoids, like other drugs or modalities such as methotrexate or PUVA, have their proper place in the management of otherwise treatment-resistant dermatologic diseases. Careful decisions as to the appropriateness of therapy will have to be made for each patient. If we maintain this attitude and also continue to carefully monitor new retinoids as they are developed, these drugs should be of great aid in clinical practice.

J. H. Epstein, M.D.: At present there is little information on the effects of systemic retinoids on photocarcinogenesis. However, we are in the process of examining the effects of oral isotretinoin in our hairless mouse system with the use of a hot quartz ultraviolet

light source. The mice are irradiated three times a week and receive 10 mg/kg of isotretinoin orally five times a week. The development of tumors greater than 4, 50, and 100 mm^3 has followed essentially the same patterns to date as expressed in Table I. As noted, by 34 weeks no significant effect of the chemical has been detected under the circumstances of this study.

Be that as it may, it has been established that tretinoin can both accelerate and inhibit photocarcinogenesis under appropriate conditions. The mechanism or mechanisms involved in either effect are not clear.

Stimulation of UV carcinogenesis might be related to effects on DNA metabolism and induction of epidermal proliferation, or immunosuppression which has been demonstrated with high doses of tretinoin. Unfortunately, there are very few data available at this time which might explain this demonstrated accelerating effect of tretinoin on photocarcinogenesis.

In contrast, there are a number of studies describing tretinoin effects which might be responsible for the inhibitory response noted. In a recent study we noted that though repeated applications of tretinoin over a 10- and 23-week period caused epidermal acanthosis, they blunted the response of the skin to acute UV injury. Thus the expected increase in DNA synthesis and hyperplastic response which occurs by 24 hours post UV irradiation was significantly suppressed.

I would suggest that if anyone does have a patient with xeroderma pigmentosum, this would be an excellent type of patient in whom the problem of UV carcinogenesis could be investigated. Of course, Dr. Peck has experience with the basal cell nevus syndrome and the multiple basal cell cancers. His studies look encouraging at least at this point.

G. G. Krueger, M.D.: I keep coming back to the question of how we should deal with our institutional review boards. Neither we nor the review boards know how to interpret the animal data, such as the data pertaining to adrenal tumors. I am wondering, Dr. Windhorst, if you could, for just a few minutes, try to take it from our point of view and tell us what we should say to an institutional review board.

D. B. Windhorst, M.D.: In the absence of a definitive reason to feel some special risk has come up requiring a study to be stopped, it is the monitor's responsibility to keep the investigator fully informed about all data that become available on the drug under study. The observation of pheochromocytomas in the chronic rat study is just as confusing and disturbing to me, raising all kinds of scientific and ethical questions, as it is to you. There is no clear way to interpret the data for applicability to humans who are being dosed in significantly different ways. My job is to keep you informed. However, the ultimate answer relates to your individual patient, and only you have the maximum information available regarding the benefit the patient is obtaining from the drug. As hard as it sounds, I think that when I play my role correctly and keep you informed, the ultimate risk/benefit judgments should rest with you and your patient, with the help of your institutional review committee.

Table I. Percent of mice with tumors greater than 50 mm^3 at the noted time periods

No. of weeks	Isotretinoin (%)*	Control (%)
24	9	13
29	13	23
34	42	39

*These mice received 10 mg/kg of isotretinoin orally 5 days a week.

J. J. Voorhees, M.D.: I would like to say that in using etretinate for psoriasis, I have not seen any improvement or any worsening in psoriatic arthritis, and if other people who have made such an observation could comment, it would be helpful for me. Also I want to return to Dr. Strauss' pivotal question about teratogenesis; I either did not understand the answer or it was not clear to me. Dr. Strauss wanted to know whether the ovum in the ovary is going to be damaged such that if a woman becomes pregnant 5 years later teratogenesis might be a problem even then. I really did not get a crisp answer to that question.

H. H. Roenigk, Jr., M.D.: I will respond to the arthritis question. Five out of our twenty patients had fairly severe arthritis. Most of them required other nonsteroidal, anti-inflammatory type drugs during the initial phases of retinoid therapy. Four out of the five were able to discontinue all of their anti-inflammatory drugs during retinoid therapy. There was significant objective and subjective improvement in arthritis. A number of the patients have come off the drug for a 3-month rest period, and at least two of the five have now had a flare of their arthritis while they were off retinoid therapy.

W. D. Stewart, M.D.: We have had a similar experience to Dr. Roenigk's. Six of our patients had psoriatic arthritis; all of them had been treated previously with antiarthritic medications. They have been treated with etretinate in a dosage level of either 25 or 50 mg/day (mostly 25 mg/day). One other point is that the onset of the disease is relatively recent in these patients, and they all have inflammatory types of arthritis. These are not patients with long-term, chronic,

deforming arthritis. All of the patients have responded quite satisfactorily and significantly to retinoid therapy.

G. Plewig, M.D.: We have had the same experience. Arthritis does improve in many patients. I also feel that the von Zumbusch pustular type of psoriasis, as well as pustular psoriasis of the Hallopeau type and the palmar-plantaris type, shows excellent improvement. The dose required for all these forms of pustular psoriasis is lower than for the chronic, stationary type.

If I might change the subject, together with Professor Schill from our department we have looked into sperm parameters in patients with conglobate acne. Almost every single patient with conglobate acne had an abnormal finding in one or several of the seven parameters in the sperm samples that were examined prior to therapy. These abnormalities all improved and came back to normal while the patients were being treated with isotretinoin. Severe inflammatory skin disease, such as Darier's disease and severe acne, can affect sperm production; this can apparently be corrected by treating the basic disease.

G. D. Weinstein, M.D.: Dr. Kamm, can you handle the teratogenicity situation.

J. J. Kamm, Ph.D.: The types of testing that we do would not directly address the question of fertilization of a "retinoid-damaged ovum" 5 years after stopping treatment. I do not think that irreversible damage to the ova in a woman can lead to teratogenesis because it seems to me that a damaged germ cell would not be fertilized or, if fertilized, would not implant. Under these circumstances, there would be no teratogenesis. However, if there were damage to the ova, this could certainly lead to decreased fertility.

G. D. Weinstein, M.D.: Didn't you say you had some data, though, in the animals receiving the drug prior to conception?

J. J. Kamm, Ph.D.: You are referring to a segment-I, reproduction/fertility study. In this type of study, treatment of the female is not stopped at the time of mating. Treatment is initiated 14 days prior to mating and is continued through parturition. There is no cessation of treatment.

G. D. Weinstein, M.D.: So we do not have any clean study in which the animals are treated prior to conception and then treatment is stopped.

J. J. Kamm, Ph.D.: The model which would have to be studied is one in which animals are mated at varying times after treatment had stopped. We have not done studies of this type.

J. S. Strauss, M.D.: Did you dose both the males and females together?

J. J. Kamm, Ph.D.: Yes. In the segment-I study, both males and females were treated.

J. S. Strauss, M.D.: So you do not have information based on administration of the retinoids, to females only before mating.

J. J. Kamm, Ph.D.: With respect to 13-*cis*-retinoic acid, there were no adverse effects on fertility or reproductive performance at the doses studied. Since there was no suggestion of any adverse effect, there was no need to determine whether males or females or both had been affected. If there had been adverse effects, then it would be a simple matter to treat males, mate them with normal females, and vice versa. The question having to do with irreversible effects on ova which are elaborated long after treatment has stopped is not addressed in any of the reproduction studies that we normally do in our laboratory.

D. B. Windhorst, M.D.: It is important to remember that isotretinoin is not mutagenic in the bacterial system.

L. A. Goldsmith, M.D.: Since it appears that some of the metabolites of etretinate could be very active, unless the bacterial system is set up for a conversion to all of its distal products, a negative study might not give you a true answer.

J. J. Kamm, Ph.D.: That is very true. However, the Ames test is designed to address the question of mutagenic metabolites. This is done by including in the assay system the so-called S9 fraction from liver which contains the drug-metabolizing enzyme system. The drug is preincubated with the liver S9 fraction, and the mixture, which contains unchanged drug and metabolites, is assayed for mutagenic potential. It can be argued that we are using S9 or drug-metabolizing system from a rat and we know that there are species, strain, and sex differences in rates of metabolism as well as in routes of metabolism. However, it is purely academic at this point since we have done carcinogenicity studies in rodents with both 13-*cis*-retinoic acid and etretinate.

A. R. Shalita, M.D.: I think the question with regard to the gametes really relates to whether or not there is any evidence of chromosomal damage. Any other effect on the ovum or on the spermatazoa would not lead to fertilization. Chromosomal damage, though, could lead to an abnormal fetus. Are there any data that chromosomal breaks or damage or anything like that occurs in animal models?

J. J. Kamm, Ph.D.: Studies with etretinate have been negative in terms of chromosome damage. I am not aware that they have been done with 13-*cis*-retinoic acid.

G. L. Peck, M.D.: Dr. Kamm, one critical question is, "At what point in time is it safe for a woman who has received etretinate to have a child?" Are there studies, for instance, in which animals that have been

treated for prolonged periods with etretinate have developed large tissue stores, and then have become pregnant at varying periods of time after stopping therapy?''

J. J. Kamm, Ph.D.: A protocol has been developed to specifically address that question in animal models. The experiment is in its planning stages now, and we intend to correlate, or try to correlate, teratogenicity with blood levels. By determining blood levels at various times after stopping treatment and initiating mating at that same time, we hope to answer the question that you are asking.

I believe that etretinate has been detected in the blood of patients for at least 6 months after stopping treatment. We do not know if this blood level would be associated with teratogenesis in animals. That is why it is a particular problem with etretinate but not with 13-*cis*-retinoic acid. With the latter you can tell the patient to wait 3 or 4 months after stopping medication, by which time 13-*cis*-retinoic acid will have cleared her system. The problem with etretinate is its prolonged half-life.

G. L. Peck, M.D.: One of the most difficult problems we have in using retinoids is the management of retinoid-induced arthralgias. Some of the approximately 5% of patients who develop arthralgias are disabled by this symptom and require high doses of anti-inflammatory agents, such as ibuprofen (Motrin) or indomethacin (Indocin). In these cases, arthralgias become a dose-limiting toxicity. Our consultant rheumatologist once refused to let us enter a patient of hers with psoriasis and psoriatic arthritis into our etretinate protocol for fear of aggravating the arthritis. The question then arises as to how the retinoids can induce arthralgias in previously symptom-free patients and yet be effective in the treatment of psoriatic arthritis.

G. Plewig, M.D.: We have seen four patients with acne fulminans accompanied by very painful arthralgias. They were put on isotretinoin, and within 2 or 3 weeks they lost their arthralgia complaints. Maybe retinoids can be used in patients with other types of arthralgias.

V. J. Derbes, M.D.: I should like to say that "arthralgia" is no more precise a term than is "headache." There are many mechanisms for joint pains as there are many mechanisms for head pain. I do not see any difficulty in observing a drug-producing pain in the one instance and relieving a type of pain in another instance.

F. L. Meyskens, Jr., M.D.: I had a few comments that you might find helpful regarding the toxicity questions that have been raised. Regarding chromosomal damage, extensive experience with many alkylating drugs in oncology generally indicates that unless you totally wipe out fertility in both males and females, normal children are produced subsequently. Secondly, regarding the liver toxicity, it is known that vitamin A produces fibrosis, which is a two-step process involving two different types of collagen. It would be very useful to determine whether the reversible or the irreversible type of collagen has been deposited in the livers of the patients that Dr. Roenigk described (monoclonal antibodies have now been developed for the five types of collagen). Thirdly, with regard to the pheochromocytoma and adrenal medullary tumors, Dr. Krueger reminded me that most of my patients die in our cancer study, and we probably have postmortems on twenty or twenty-five patients; some of these patients had received the drug for significant amounts of time. So one of the first things I want to do when I get back home is to look at the postmortems to see if there are any unexpected tumors present.

D. B. Windhorst, M.D.: Just a comment on your plan to go back and do some examinations of your autopsy material: it would be useful to write down a set of possible observations and associated conclusions you might make before you look at the material because your patients probably had received multiple potentially toxic drugs. Unless you specify in advance what you might observe, and then say what that finding is going to mean to you, you can end up not knowing what to make of your data.

C. N. Ellis, M.D.: We talked about combination therapy for psoriasis at length earlier. What combination therapies have been used in Europe or elsewhere for the other disorders of keratinization? Wouldn't combinations be expected to lower the risks of the retinoid therapy?

G. D. Weinstein, M.D.: Dr. Plewig, do you treat ichthyosis or Darier's disease with any combinations that include retinoids?

G. Plewig, M.D.: I know of no controlled studies for ichthyosis or other disorders of keratinization in which two drugs were given systemically at the same time. Of course, topically we try various combinations like tar, anthralin, and ultraviolet light in combination with isotretinoin or etretinate.

E. M. Farber, M.D.: I would like to ask the panel a question regarding the elevation of the blood triglycerides. Has anyone had experience in placing patients on a strict low animal fat diet and then resuming retinoid therapy.

T. P. Nigra, M.D.: I have had experience in the young 13-year-old boy, as previously mentioned. We monitored him and when we felt he was not cheating, we found that his triglycerides were down. At that age it is difficult to stay on a diet, and many times his

triglycerides were elevated, which we believe was due to noncompliance. So, my impression is that diet would help a great deal in the use of this drug if one could obtain compliance.

C. N. Ellis, M.D. The normal variability of triglycerides in patients must be kept in mind. During an 8-week placebo period in nine of our psoriatic patients, six (67%) had serum triglyceride levels which exceeded a single initial measurement by 20% or more. Of six patients with initially normal triglyceride levels, such variation during the placebo period resulted in two (33%) actually exceeding the upper limit of normal. These data indicate the necessity for adequate pretherapy or placebo monitoring of patients.

T. P. Nigra, M.D.: I might make another point, and that is that there are other drugs which do raise triglycerides. Systemic steroids and estrogens will do this. How often do we pause when we give someone systemic steroids to think about the triglyceride elevation?

J. S. Strauss, M.D.: I would like to go back to the question that Dr. Voorhees brought up relative to hormonal action of the retinoids. I wonder whether potential hormonal activity was looked at as part of the pharmacologic studies by Hoffmann-La Roche.

J. J. Kamm, Ph.D.: We have not studied hormonal activity as part of our long-term toxicity studies.

J. S. Strauss, M.D.: Have the oral retinoids been tested for androgenic, progestational, or estrogenic activity?

J. J. Kamm, Ph.D.: Not to my knowledge.

D. S. Goodman, M.D.: Let me first comment about the hypertriglyceridemia as related to steroid hormone action. It is now well established that women on contraceptive pills have, on average, higher lipid levels than women not on the pill. The main effect is due to the estrogen component of this contraceptive medication. As I mentioned earlier, there is considerable uncertainty at the moment about the clinical significance of hypertriglyceridemia in the lipidology field. With regard to dietary treatment of elevated triglycerides (and exactly what one considers an elevated triglyceride level is now a little bit uncertain), the current generally agreed upon thinking is that the most important variable is control of caloric intake, not of the distribution of calories amongst foodstuffs. This is particularly true for obese, overweight people. And by overweight I don't only mean obviously obese people, because you can often find someone who is a little bit overweight, put them on a calorically restricted diet to lose ten pounds, and find a dramatic decrease from a triglyceride of about 300 mg/dl down to 200 or less. Moreover, there is a great heterogeneity among different people with regard to sensitivity of triglyceride level to caloric flux. So, the main element that is now felt to be important in regard to dietary treatment of hypertriglyceridemia is control of calories. For this, you should use the same fat-controlled diet which is used for hyperlipidemia in general, namely, a cholesterol-restricted intake (less than 300 mg/day) and a fat intake of about 35% of total calories with no more than 10% of calories as saturated fats. The old thought about restricting carbohydrates for hypertriglyceridemia is definitely not now felt to be the proper approach. There are much data, in fact, that for the vast majority of patients carbohydrate restriction is definitely not desirable.

D. West, M.S.: Could Dr. Windhorst or perhaps Dr. Plewig or anyone else on the panel share with us the reported side effects attributable to the oral retinoids that we have not discussed to date. Perhaps there are none?

G. Plewig, M.D.: One side effect of isotretinoin which has not been discussed here and which has caused some problems and dropouts in our studies is migrating arthralgia and myalgia. All of a sudden patients develop severe joint pain, usually of the big joints, shoulder, knee, or hip, or in the truncal muscles. It is not dose-related. We have seen it with the lowest dose of 0.1 mg/kg/day and also in the highest dose of 2 mg/kg/day. It persists for days or weeks and seems to occur mainly in patients who do vigorous physical exercise. We had athletes and farmers who developed the symptoms. I have no explanation at present for this phenomenon, and I wonder if you have seen this symptom. This is with isotretinoin; we have not seen it with etretinate.

D. B. Windhorst, M.D.: The data on all U.S. patients who have received isotretinoin (grouping all musculoskeletal complaints together) indicate that there is a 20% incidence of musculoskeletal complaints.

J. G. Marks, Jr., M.D.: This is directed to Dr. Roenigk. Your study of liver biopsies from patients on etretinate did not have controls. Would you put in perspective what you would predict would have happened in this group of patients if they were not treated? I realize that clinical investigation committees would probably not look favorably on doing serial liver biopsies in a control group.

H. H. Roenigk, Jr., M.D.: You could consider that the patients serve as their own controls, and it is prospective in the sense that they do have pretreatment liver biopsies. We personally do have a vast experience with methotrexate, and there are many papers in the literature on liver biopsies done in psoriatic patients not treated with methotrexate. Variable changes are seen in

these patients, and I do not know that there is an answer to your question. I think that there are certain other toxic exposures that patients experience. People get hepatitis, people are exposed to alcohol, there is muscle damage, etc., all of which can affect the liver. For example, one of our patients went from fibrosis to cirrhosis; we are fairly certain this was due to alcohol ingestion because he admitted that he was a heavy drinker and also was using some other nonapproved drugs. He has had Mallory bodies in the liver biopsy to support this. No one has taken the general population of psoriasis patients and followed them for 3 years with liver biopsies every year. I do not think that study will ever be done.

J. G. Marks, Jr., M.D.: What were the morphologic changes in the liver in animals that were given the same dosage as would be given to humans?

H. H. Roenigk, Jr., M.D.: We have looked into this, but there is no animal model with methotrexate that produces liver damage similar to what is seen in humans.

E. M. Farber, M.D.: There is the growing demand for retinoid therapy in psoriasis. Is there any experience with the use of isotretinoin in psoriasis? Does it work at all? This is important because if isotretinoin becomes available commercially soon, then of course there will be a large demand that it be used for treatment of psoriasis. What is the comparison of the two retinoids in the management of psoriasis?

G. L. Peck, M.D.: Originally, isotretinoin was used in psoriasis by Runne et al (*Arch Dermatol Forsch* **247:**171, 1973.). They felt that it was not really of value, considering the side effects that were produced when it was used alone. In my series of eight patients, half improved and half did not. The question remains, though, once it is available by prescription whether it could be useful in a combination therapy program.

E. M. Farber, M.D.: I am surprised that isotretinoin has been dropped as a therapeutic agent for psoriasis with such a limited clinical testing period. Dr. Peck speaks of eight patients plus the studies by Dr. Orfanos. Has anyone else tried this?

G. Plewig, M.D.: I can support Dr. Peck. Isotretinoin, as a single agent, is much less effective than etretinate in controlling psoriasis. We do not use isotretinoin for the treatment of psoriasis, be it alone or in combination. All of the combination treatment schedules in Europe reported so far have involved the use of etretinate. Many combinations have been studied. In our department the use of the Goeckerman or the Ingram technics, as well as the short-term application of anthralin for 20 minutes, is being evaluated. Of course, we have combined etretinate with PUVA in certain instances.

A. J. Miller, M.B., B.S., M.R.C.P.: Concerning unreported side effects with etretinate, I have had two patients reported to me who developed edema, one peripheral edema, the other peripheral and pulmonary edema. Considering the number of patients who have been exposed to this drug in the United Kingdom in the last 2 years, this is not very common. It appeared to be a drug effect in that it disappeared upon cessation of treatment and returned on re-exposure to the drug. Furthermore, I have seen today for the first time, unbeknown to me, that this is also a feature of hypervitaminosis A.

K. M. Halprin, M.D.: In terms of inhibition of spermatogenesis, are there data on how long this lasts. Are there any data to indicate that abnormal fetuses can result from the mating of a treated male animal with a normal female animal?

D. B. Windhorst, M.D.: In more than sixty patients evaluated before and after treatment, we have no indication that there is any effect on sperm motility or count. Therefore, in the human at the doses of isotretinoin that we are giving, we find no evidence of any abnormality related to therapy. There are similar negative data with etretinate therapy. The animal findings followed the administration of much larger doses.